# Hepatitis C virus recurrence occurs earlier in patients receiving donation after circulatory death liver transplant grafts compared with those receiving donation after brainstem death grafts

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**TITLE PAGE**

**Manuscript title:** HCV recurrence occurs earlier in patients receiving donation after circulatory death (DCD) liver transplant compared with those receiving donation after brainstem death (DBD) grafts.

My manuscript is submitted as an original works: This article reports the experience of the UK's largest liver transplant centre of patients receiving donation after circulatory death (DCD) liver grafts and compares their outcomes to a matched cohort of individuals receiving donation after brainstem death (DBD) liver grafts for hepatitis C related liver disease. We compare and report 5 year patient and graft survival, HCV recurrence, and risk factors for recurrence in the two cohorts, and discuss the implications in an era of effective anti-viral therapy and organ shortage for transplantation. Many thanks for considering this article for publication.

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**Key words:**
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Donation after brainstem death liver transplant
Donation after circulatory death liver transplant

**Abbreviations:**
CMV cytomegalovirus
DAA direct acting antiviral
DBD donation after brainstem death
DCD donation after circulatory death

HAT hepatic artery thrombosis
HCC hepatocellular carcinoma
HCV hepatitis C virus
LFT liver function test
MELD model for end-stage liver disease score
OLT orthoptic liver transplantation
SD standard deviation
SVR sustained virological response
UKELD United Kingdom model for end-stage liver disease

**Tables:** 3

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*Abstract

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**Abstract**

**Introduction**: HCV-related cirrhosis remains the commonest indication for liver transplantation worldwide, yet few studies have investigated the impact of DCD graft use on HCV recurrence and patient outcomes. DCD grafts have augmented the limited donor organ pool and reduced wait-list mortality, although concerns regarding graft longevity and patient outcome persist.

**Methods**: This was a single centre study of all HCV+ adults who underwent DCD liver transplantation between 2004 and 2014. 44 HCV+ patients received DCD grafts, and were matched with 44 HCV+ recipients of DBD grafts, and their outcomes examined.

**Results**: The groups were matched for age, sex, presence of HCC; no significant differences were found between the group's donor or recipient characteristics. Paired and unpaired analysis demonstrated that HCV recurrence was more rapid in recipients of DCD organs compared with DBD grafts (408 vs 657 days; p=0.006). There were no significant differences in graft survival, patient survival, or rates of biliary complications between the cohorts despite DCD donors being 10 years older on average than those used in other published experience.

**Conclusions**: In an era of highly effective DAA therapy, rapid HCV recrudescence in grafts from DCD donors should not compromise long term morbidity or mortality. In the context of a rising wait-list mortality it is prudent to use all available sources to expand the pool of donor organs, and our data supports the practice of using extended-criteria DCD grafts based on donor age. Notwithstanding that,

clinicians should be aware that HCV recrudescence is more rapid in DCD recipients, and early post-transplant anti-viral therapy is indicated to prevent graft injury.

**Highlights**

- This article reports the experience of the UK's largest liver transplant centre of patients receiving donation after circulatory death (DCD) liver grafts and compares their outcomes to a matched cohort of individuals receiving donation after brainstem death (DBD) liver grafts for hepatitis C related liver disease.
- HCV recurrence was more rapid in DCD recipients; other risk factors were CMV infection and steroid use post-transplantation.
- 5-year patient and graft survival, and rates of biliary complications, were equal in both groups.
- On average DCD donor age was 10 years older than in other published cohorts, supporting the uses of extended-criteria DCD grafts.
- In an era of highly effective DAA therapy, rapid HCV recrudescence in grafts from DCD donors should not compromise long term morbidity or mortality, but clinicians should be aware that early post-transplant anti-viral therapy is indicated to prevent graft injury.

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**Introduction**

Orthoptic liver transplantation (OLT) is a life-saving intervention for patients with end-stage liver disease, but the availability of transplantation is limited by the number of organs available. Current NHS waiting list mortality is approximately 17% in the UK with the highest on-list mortality occurring in the first 6 months after listing and, whilst the number of patients registered for transplantation continues to rise, the number of conventional DBD livers available for grafting has remained relatively static (1). The increased use of donation after circulatory death (DCD) organs is a pragmatic response to the problem and seeks to implant livers that would previously not have been available for transplantation and, by increasing the available donor pool, seeks to reduce patient mortality and shorten the time to transplantation on waiting lists (2-5). Notwithstanding this, despite growing expertise in the selection and use of DCD grafts, there are concerns regarding a perceived inferior medium and long term graft and patient survival in DCD recipients, particularly in those DCD grafts harvested from older donors (6).

In the UK, liver disease secondary to hepatitis C virus (HCV) infection and/or alcohol use remain the primary indications for liver transplantation (1). Few studies however have investigated the impact of DCD graft use on recurrence of HCV and long-term outcomes.

Birmingham is the largest liver transplant unit in Europe, grafting approximately 250 patients per year, and has the highest rate of graft utilisation in the UK (1). There has been steady growth in the utilisation of DCD grafts, such that 29% of adult liver transplants undertaken in Birmingham in 2015 used DCD-derived livers. Transplantation for hepatitis C related cirrhosis comprises 14% of all indications for liver replacement in Birmingham. Between January 2004 and 2014, 208 DCD grafts were used for liver transplantation (15% of total transplant activity), and 49 of these were for HCV related liver disease.

We retrospectively examined the outcomes of all HCV positive patients undergoing DCD liver transplantation, and compared them with a matched cohort of HCV positive patients receiving donation

after brainstem death (DBD) grafts. Particular attention was paid to patient and graft survival, HCV recurrence, and biliary complications.

**Methods**

This was a retrospective matched case-controlled single centre study of all HCV positive adults who underwent controlled (Maastricht III) DCD liver transplantation between January 2004 and January 2014 at the Queen Elizabeth Hospital, Birmingham. Of the 1384 adult transplants completed in this period, DCD grafts were used in 208 patients, 49 for HCV related liver disease. Five patients were excluded because they were found to have been successfully treated for HCV prior to transplantation. A cohort of 44 HCV positive patients who received DCD grafts was identified and matched with 44 HCV positive recipients of DBD grafts during the same time period. Patients were matched with regards to age, sex, and the presence of hepatocellular carcinoma (HCC).

Other characteristics compared between the two groups were donor age, model for end-stage liver disease score (MELD), the United Kingdom model for end-stage liver disease (UKELD) score at time of transplantation, HCV genotype and viral load, use of renal replacement therapy post-operatively, episodes of rejection, and use of antiviral treatment pre-and post-transplantation. Outcomes measured were patient and graft survival, time to HCV recurrence, and biliary complications (ischaemic cholangiopathy, anastomotic strictures, bile leaks).

The primary endpoint was HCV recurrence and secondary endpoints were patient and graft survival, and biliary complications. The diagnosis of HCV recurrence was made with positive HCV PCR supported by either biopsy findings (chronic portal inflammation, with or without portal lymphoid aggregates, together with necroinflammatory and ductular-type interface activity) (7), or, in the context of

significantly abnormal liver function tests (LFTs) (bilirubin>30mg/dL, AST>100units/L), a high HCV titre and a high level of clinical suspicion. Biopsies were not routinely performed unless clinically indicated.

All patients were initially treated with triple immunosuppression therapy including a calcineurin inhibitor (tacrolimus or cyclosporine), anti-proliferative agent (mycophenolate mofetil or azathioprine) and steroids (hydrocortisone in the immediate post-operative days followed by conversion into prednisolone 20 mg/ day tapered over 3 months).

Episodes of rejection requiring augmentation of steroid dose were recorded. HCV recurrence was treated according to clinical need with the standard of care therapy that existed at that time - either dual therapy (interferon and ribavirin), triple therapy (interferon, ribavirin and telapravir) or using regimens of direct acting antiviral therapy.

**Statistical Analysis**

Recipient and donor characteristics were compared among the groups using Fisher's exact test for categorical variables and Student's t-tests or Mann-Whitney tests, as appropriate, for continuous variables. Values are expressed as frequencies and percentages for categorical data, and mean and standard deviation (SD), or median and interquartile range for continuous data.

Patient survival, graft survival, and HCV recurrence among the patient groups were compared with Kaplan-Meier plots and log-rank tests. Graft survival was timed from the date of transplantation to the date of re-transplantation or death (whichever came first) and was censored for the date of the end of the study period or for the date of the last correspondence for patients lost to follow-up. Patient survival was time from the date of transplantation to the date of death and was censored for the date of the end of the study period or for the date of the last correspondence for patients lost to follow-up. HCV

recurrence was timed from the date of transplantation to the date of diagnosis and was censored for the date of the end of the study period or for the date of the last correspondence for patients lost to follow-up, the date of death, or the date of re-transplantation.

Unconditional and conditional Cox regression were used in the univariate analysis of predictors of patient survival, graft survival, and HCV recurrence.

Biliary complications were compared between the two groups using Fisher's exact test.

Significance was defined at a P value < 0.05. Data were analysed using IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.

**Results**

The two groups were well matched for age, sex, and presence of HCC. The mean age at transplant was 55 years; 70 of 88 (80%) patients were male. No significant differences were found between the groups for donor age, HCV genotype, CMV infection post-transplant, immunosuppression regimens, and rates of rejection requiring steroids (see table 1). The Model for End-Stage Liver Disease (MELD) score at transplantation was higher in DBD recipients than those receiving DCD grafts (median=13 versus 10; p=0.282) which would be consistent with our usual practice of offering DCD grafts to recipients with higher levels of fitness and physical functionality. As one might expect, this cohort had a lower UKELD score, and the difference between the groups was statistically significant (median=52 versus 50; p=0.020, see table 1).

Overall the patients were followed up for a median of 3.8 years (range 1.1-12.6). Five year patient survival was 77.3% and 72.2% for DCD and DBD recipients, respectively (p=0.709). Five year graft survival was 70.2% for DCD recipients, versus 75.0% for DBD recipients (p=0.802). Causes of death were

HCC recurrence in nine patients, sepsis or pneumonia in six, recurrent hepatitis C in four, brain death in two, and multiple causes for the remaining seven patients (see table 2). The cause of death is unknown for two patients. Seven patients had early graft failure post-transplantation (range 2 days to 3 months) and all were successfully re-grafted. Four were DBD grafts; two failed secondary to refractory acute cellular rejection within one month of transplantation, the third developed early hepatic artery thrombosis (HAT) and there was primary non function in the forth. Two DCD grafts failed secondary to primary non function and the third also had early HAT.

Rates of biliary complications were low and comparable between the two cohorts, with a slightly increased incidence of ischaemic cholangiopathy in the DCD recipient cohort, not reaching statistical significance (p=0.594).

Paired and unpaired analysis demonstrated that HCV recurrence was more rapid in recipients of DCD compared with DBD grafts (408 versus 657 days; p=0.006). CMV infection (p=0.021) and rejection requiring steroid augmentation (p=0.030) were both risk factors for recurrence. There was no difference in HCV recurrence rate between viral genotypes on direct comparison between paired genotypes or all four groups (p=0.118).

Twenty-six patients had aggressive HCV recurrence (recrudescence within one year of transplantation requiring antiviral therapy) and were reviewed in greater detail. Use of DCD grafts (p=0.010), as well as CMV infection (p=0.001) were again showed to be risk factors for recurrence in this cohort. No other factors were found to found to be significant for aggressive recurrence, including recipient age (p=0.237), sex (p=0.248), genotype (p=0.233), MELD score at the time of transplantation (p=0.615), viral load pre transplant (p=0.451), or viral load at one year post transplant (p=0.836), or even steroid use (p=0.070).

Of the total 88 patient cohort, seven patients had CMV infection, all within 5 months of transplantation. Six of these patients were CMV positive prior to transplantation and all received organs from CMV positive liver donors. It was unclear whether the CMV negative recipient was compliant with prophylactic valganciclovir. One patient who developed abnormal LFTs was treated successfully with valganciclovir, another was treated for CMV colitis; in four patients the infection was considered clinically insignificant and treatment was not initiated; it is unclear whether the remaining patient was treated.

12 patients had acute cellular rejection requiring steroid augmentation at a median of 7 days post-transplant (range 2 days – 16 months). All 12 patients had received standard immunosuppression and had acceptable serum tacrolimus levels prior to the episode of rejection, except one patient who developed acute rejection at 16 months secondary to poor medication compliance, and one patient for whom tacrolimus initiation post-transplant was delayed.

Forty-eight patients received antiviral treatment prior to transplantation (21 DBD recipients and 27 DCD recipients); all had treatment failure (poor viral response, post-treatment relapse, treatment intolerance or liver decompensation). Thirty-one patients did not receive treatment (15 DBD recipients, 16 DCD recipients), and for 9 patients pre-transplantation treatment status was unclear from electronic records (8 of whom were DBD recipients).

Post-transplantation, 44 patients have received 46 courses of antiviral therapy. Among the 44 DBD liver recipients, 1 patient received single therapy with interferon, 10 received dual therapy (interferon or PEG-interferon and ribavirin), 7 received triple therapy (PEG-interferon, ribavirin, telapravir or PEG-interferon, ribavirin, sofosbuvir), 1 received dual therapy followed by triple therapy, and 2 have completed treatment with direct antiviral therapy (DAA). A sustained virological response (SVR) was achieved in 14 of the 21 (66.7%) DBD recipients that were treated within the study period. For those

patients who received DCD grafts, 10 patients received dual therapy, 10 received triple therapy, and 6 patients have completed DAA therapy, including 2 patients who received dual therapy followed by DAAs, and one who received triple therapy and DAAs. SVR was achieved in 17 of 23 patients (73.9%). It is worth noting that the majority of these patients were treated in a pre-DAA era.

Twenty-six patients were considered to have early aggressive recurrence (abnormal liver function with positive viral titre and evidence of fibrosis) within 2 years of transplantation. Fourteen were successfully treated with antiviral therapy and none of these patients have subsequently experienced liver related mortality or morbidity, other than one patient who developed recurrent HCC and died 5 years post-transplant. Nine patients failed antiviral therapy; 3 died as a result of recurrent HCV at a mean of 500 days post-transplantation (range 192-947 days), 1 died due to recurrent HCC, 1 died from gastrointestinal bleed, 2 were reassessed for liver transplantation, one of whom was relisted, and both are still alive. Three patients were not treated; 1 has died of HCC recurrence, 1 is alive, and 1 lives abroad. No patients in this cohort have required re-transplantation for HCV recidivism.

**Discussion**

HCV related liver disease remains the primary indication for liver transplantation worldwide. Survival is known to be worse than other indications for liver replacement, primarily due to HCV recrudescence shortening graft survival (8). We are already seeing how highly effective direct acting antiviral therapy reduces short to medium term morbidity mortality in both pre and post-transplant populations, and is likely that over the next 10 years patient and graft survival should rise to match the best outcomes achieved in liver transplantation for other indications. Nevertheless, demand for organs remains high and grafts that were once considered more marginal (such as DCD-derived organs) provide a valuable resource that will help to reduce wait-list times and mortality.

Few studies have evaluated the effect of DCD liver organs in HCV positive recipients. A recent meta-analysis by Wells et al included only 3 single centre studies with mixed outcomes (9). One of those was a retrospective study carried out by Taner et al, which compared 77 HCV positive DCD liver recipients with 77 matched DBD recipients and showed no difference in graft or patient survival between the two groups. Multi-variate analysis demonstrated that a higher MELD score and the occurrence of CMV infection within the first year of transplantation reduced survival in all recipients: genotype 1 infection and moderate to severe rejection were both risk factors for the development of stage 2 fibrosis post-transplantation, but these risks were not specifically associated with the use of DCD grafts (10). A similar but smaller study by Tao et al suggested a trend toward poorer outcomes in DCD liver recipients compared with the DBD cohort, but statistical significance was not reached, and no difference in HCV recurrence was seen between the two matched groups. CMV infection and acute cellular rejection did increase the risk of HCV recurrence in both groups, as well as donor age (11).

Only the paper by Hernandez-Alejandro, which reported the outcomes of 17 DCD HCV positive liver recipients, suggested a significantly reduced graft survival, as well as increased HCV recurrence in these

patients (12). Interestingly, Wells' meta-analysis concluded that the rates of primary non-function were higher in HCV positive recipients of DCD grafts compared to DBD grafts, but that overall graft and patient survival, biliary complications, and HCV recurrence rates, were equivalent (9).

These findings are further supported by a retrospective study of two large US databases, the United Network for Organ Sharing and the Organ Procurement and Transplantation Network, which demonstrated inferior outcomes for all patients receiving DCD grafts compared with DBD grafts, but the difference between the groups was less significant for the HCV positive cohort compared with HCV negative recipients with other indications for liver transplantation (6). A similar study interrogating the outcomes of all liver recipients at our centre demonstrated that rates of ischaemic cholangiopathy and acute kidney injury were higher in DCD recipients, but that there was no difference in graft or patient survival within a matched cohort (13).

Our results for graft and patient survival are consistent with other single centre retrospective studies, but show more rapid HCV recrudescence in DCD recipients. This was reflected in a higher proportion of those individuals requiring DAA therapy. CMV infection and steroid augmentation for episodes of rejection were both risk factors for HCV recrudescence, as has been previously demonstrated. There were no differences between the rates of primary non-function or acute kidney injury, although there was a trend towards increased rates of biliary complications in the DCD cohort which would fit with published experience; that the differences were not more stark is probably a reflection of system learning and improved patient selection in DCD graft recipients which has minimised the impact on graft survival and limited post-op complications.

It is worth noting that the mean DCD (and DBD) donor age in our study was over 10 years older than the studies carried out by Taner and Tau (48.0 years for DBD grafts and 49.3 years for DCD donors in our study, compared with 37.6 and 37.7 years in Taner's study, and 38.1 and 37.9 years in the paper by Tau

et al, for DBD and DCD grafts, respectively (10, 11)). Despite using more extended-criteria grafts, we have demonstrated comparable long term outcomes, demonstrating that it is safe to extend DCD (and DBD) criteria by using liver-grafts taken from older donors.

We recognise that our study has the limitation of being a moderate-sized, single centre retrospective analysis, but the well matched groups and uniformity of surgical practice have resulted in a detailed analysis that provides compelling evidence to support the premise that the use of DCD organs in HCV positive recipients is both justifiable and safe.

**Conclusions**

In the era of potent DAA therapy, rapid HCV recrudescence in grafts from DCD donors should not compromise long term morbidity or mortality. HCV remains the primary reason for liver transplantation worldwide and, in an era of burgeoning wait-list mortality, it is prudent to use all available sources to expand the pool of donor organs, including use of grafts from donation after circulatory death. Clinicians should be aware that HCV recrudescence is more rapid in this group and that early post-transplant anti-viral therapy is indicated to prevent graft injury. The use of DCD livers provides an invaluable pool of organs which, with improvements in graft preservation, will provide equivalent outcomes to HCV+ patients receiving conventional DBD livers.

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Table 1. Characteristics of HCV positive recipients of DCD and DBD donors

| **Characteristic** | **DCD (n=44)** | **DBD (n=44)** | **p Value** |
|---|---|---|---|
| Recipient Age | 55.4 (+/-6.5) | 55.2 (+/-6.7) | 0.917 |
| Recipient gender M:F | 35(80%): 9 (20%) | 35 (80%): 9 (20%) | 1.000 |
| HCC in explant | 25 | 25 | 1.000 |
| MELD score | 10 (8-18) | 13 (10-17) | 0.282 |
| UKELD | 50 (46-55) | 52 (50-55) | 0.020 |
| HCV Genotype | | | 0.118 |
| 1 | 17 | 20 | |
| 2 | 2 | 0 | |
| 3 | 24 | 19 | |
| 4 | 0 | 3 | |
| Viral Load at transplantation | 626997 (215-2030007) | 70055 (3727-341383) | 0.044 |
| Donor age (yrs) | 49.3 (+/-16.2) | 48.0 (+/-13.5) | 0.685 |
| Incidence of Primary non-function | 2 | 3 | 1.000 |
| Days in ITU post–transplant | 3 (2-4) | 3 (2-4) | 0.997 |
| Renal Replacement Therapy post-transplant | 8 (18%) | 12 (27%) | 0.446 |
| Episodes of rejection requiring steroids | 7 (15.9%) | 5 (11.4%) | 0.757 |
| CMV infection within 1$^{st}$ year of transplantation | 4 | 3 | 1.000 |
| Biliary complications (total) | 8 | 5 | 0.549 |
| Ischaemic cholangiopathy | 5 | 1 | 0.202 |
| Strictures | 3 | 2 | - |
| Other | 0 | 2 | - |
| Number of biopsies taken | 34 | 25 | 0.069 |

Table 2. Causes of death for DBD and DCD recipients

| **Cause of death** | **DBD recipient** | **DCD recipient** |
|---|---|---|
| Recurrent HCC | 4 | 5 |
| Recurrent Hepatitis C | 2 | 2 |
| Sepsis/pneumonia | 4 | 2 |
| Hepatic artery thrombosis | 0 | 1 |
| Chronic rejection | 0 | 1 |
| Brain death | 2 | 0 |
| Renal failure | 0 | 1 |
| Gastrointestinal bleed | 1 | 0 |
| Ischaemic heart disease | 0 | 1 |
| De novo malignancy | 1 | 0 |
| Suicide | 0 | 1 |
| Unknown | 1 | 1 |

Table 3. Antiviral treatment post-transplant

| **Treatment** | **DBD recipient** | **DCD recipient** | **SVR achieved** |
|---|---|---|---|
| Single therapy | 1 | 0 | 0 |
| Duel therapy | 10 | 10 | 11 |
| Triple therapy | 7 | 10 | 12 |
| DAAs | 2 | 6 | 8 |

Figure 1. Patient survival in DBD versus DCD recipients

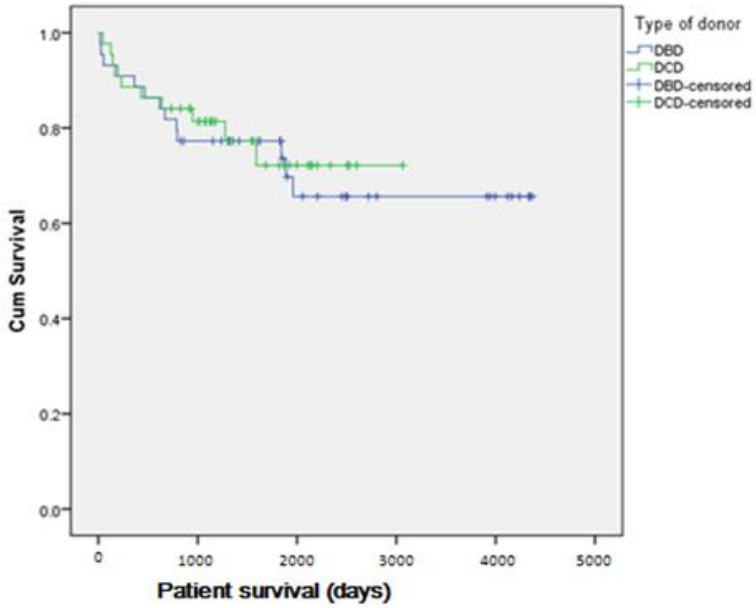


Figure 2. Graft survival in DBD vs DCD recipients

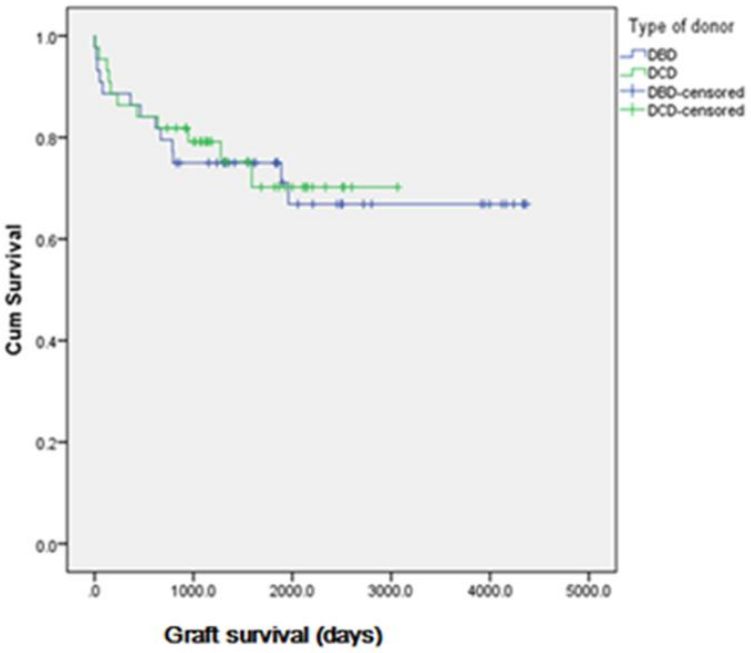
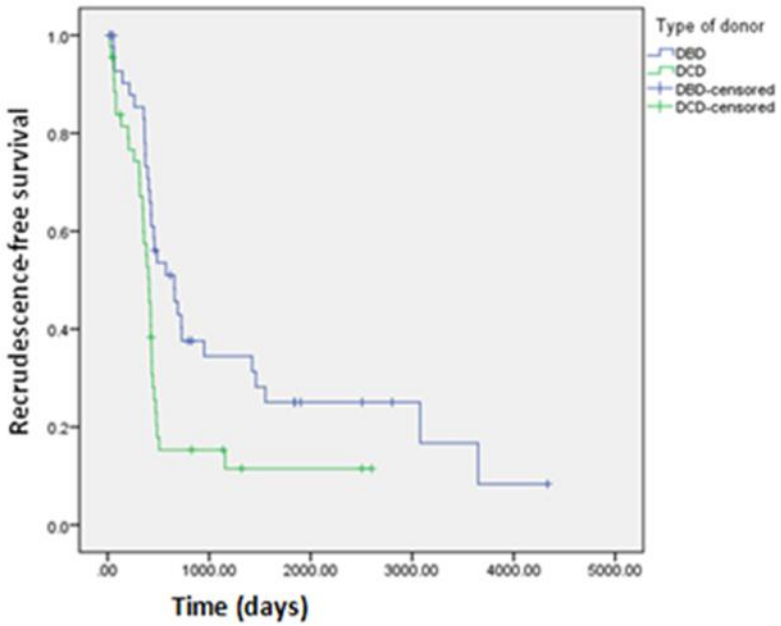



Figure 3. Hepatitis C recrudescence in DBD vs DCD recipients



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## 1. Identifying information.

## 2. The work under consideration for publication.

This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking "No" means that you did the work without receiving any financial support from any third party -- that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check "Yes".

## 3. Relevant financial activities outside the submitted work.

This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. You should disclose interactions with ANY entity that could be considered broadly relevant to the work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

## 4. Intellectual Property.

This section asks about patents and copyrights, whether pending, issued, licensed and/or receiving royalties.

## 5. Relationships not covered above.

Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.

### Definitions.

**Entity:** government agency, foundation, commercial sponsor, academic institution, etc.
**Grant:** A grant from an entity, generally [but not always] paid to your organization
**Personal Fees:** Monies paid to you for services rendered, generally honoraria, royalties, or fees for consulting , lectures, speakers bureaus, expert testimony, employment, or other affiliations
**Non-Financial Support:** Examples include drugs/equipment supplied by the entity, travel paid by the entity, writing assistance, administrative support, etc.
**Other:** Anything not covered under the previous three boxes
**Pending:** The patent has been filed but not issued
**Issued:** The patent has been issued by the agency
**Licensed:** The patent has been licensed to an entity, whether earning royalties or not
**Royalties:** Funds are coming in to you or your institution due to your patent

# ICMJE Form for Disclosure of Potential Conflicts of Interest

## Section 1. Identifying Information

1. Given Name (First Name): Sarah
2. Surname (Last Name): Townsend
3. Date: 20/02/2017

4. Are you the corresponding author? ☒ Yes ☐ No

5. Manuscript Title: HCV recurrence is more aggressive in patients receiving donation after circulatory death (DCD) liver transplant compared with those receiving donation after brainstem death (DCD) grafts

6. Manuscript Identifying Number (if you know it):

## Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☒ No

## Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were **present during the 36 months prior to publication**.

Are there any relevant conflicts of interest? ☐ Yes ☒ No

## Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☒ No

# ICMJE Form for Disclosure of Potential Conflicts of Interest

## Section 5. Relationships not covered above

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

☐ Yes, the following relationships/conditions/circumstances are present (explain below):

☒ No other relationships/conditions/circumstances that present a potential conflict of interest

At the time of manuscript acceptance, journals will ask authors to confirm and, if necessary, update their disclosure statements. On occasion, journals may ask authors to disclose further information about reported relationships.

## Section 6. Disclosure Statement

Based on the above disclosures, this form will automatically generate a disclosure statement, which will appear in the box below.

## Evaluation and Feedback

Please visit http://www.icmje.org/cgi-bin/feedback to provide feedback on your experience with completing this form.

*Letter to Editor

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May 15th 2017

Dear Dr Kahan,

Thank you for the feedback regarding the recently submitted manuscript "HCV recurrence is more aggressive in patients receiving donation after circulatory death (DCD) liver transplant compared with those receiving donation after brainstem death (DBD) grafts," and for the opportunity to make changes to the article. We have made revisions to the manuscript, as detailed below, and agree that these improve the manuscript.

Editorial comments/reviewer 1:

1. "**The title. This is a very nice study but it in no way suggest that HCV recurrence is more aggressive. It just occurs somewhat earlier.**" The title has been changed to "HCV recurrence occurs earlier in patients receiving donation after circulatory death (DCD) liver transplant compared with those receiving donation after brainstem death (DBD) grafts"

2. "**Please do not embed the Tables/Figures within the text, rather place them AFTER the References."** The tables and figures have been removed and placed at the end of the manuscript.

The manuscript has also been altered to ensure double spacing throughout, and as a letter document as requested.

Thank you once again for considering our manuscript. We look forward to hearing from you.

With kind regards

Dr Sarah Townsend

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# MANUSCRIPT RECEIPT - FINANCIAL AGREEMENT

Title Page With ALL Author Email Addresses: _Y_____

Submitted Text Pages: 16_____

Submitted Tables: 3_____ **Abstract Included** _Y_____

Submitted Figures: 3_____

**Total Pages Submitted (excluding Title Page and Abstract):16_____**

Manuscript Title: (PLEASE TYPE)

HCV recurrence is more aggressive in patients receiving donation after circulatory death (DCD) liver transplant compared with those receiving donation after brainstem death (DBD) grafts.

**By submission of this manuscript to *Transplantation Proceedings*, I acknowledge I have read the Guidelines to Authors of Manuscripts Submitted As an Original Work and agree with the contents, and that I have attached a completed and signed Authorship And Conflict Of Interest Statement (ACIS) on behalf of each author listed on this manuscript.**

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